Fiscal Year:	FY 2023	**Task Last Upd**	
PI Name:	Goukassian, David A M.D., Ph.D.		
Project Title:	Space Relevant Radiation-Induced Cardiovascular Disease Risk Thresholds: Effect of Gender on the Outcome		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:			
Joint Agency Name:		**TechPort:**	
Human Research Program Elements:	(1) **SR**:Space Radiation		
Human Research Program Risks:	(1) **Cardiovascular**:Risk of Cardiovascular Adaptations Contributing to Adverse Mission Performance and Health Outcomes		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
PI Email:	david.goukassian@mssm.edu		
PI Organization Type:	UNIVERSITY	**P**	
Organization Name:	Icahn School of Medicine at Mount Sinai		
PI Address 1:	Zena & Michael A. Weiner Cardiovascular Institute		
PI Address 2:	One Gustave L. Levy Place, Box 1030		
PI Web Page:			
City:	New York		
Zip Code:	10029	**Congressional Di**	
Comments:	NOTE: PI moved to Icahn School of Medicine at Mount Sinai from Temple University in October 2018.		
Project Type:	GROUND	**Solicitation / Funding So**	
Start Date:	04/10/2019	**End**	
No. of Post Docs:	3	**No. of PhD Deg**	
No. of PhD Candidates:	2	**No. of Master' De**	
No. of Master's Candidates:	1	**No. of Bachelor's De**	
No. of Bachelor's Candidates:	1	**Monitoring Ce**	
Contact Monitor:	Elgart, Robin	**Contact P**	
Contact Email:	robin.elgart@nasa.gov		
Flight Program:			
Flight Assignment:	NOTE: Continuation of "Space Relevant Radiation-Induced Cardiovascular Disease Risk Thresholds: Effect of Gender on the Outcome," grant 80 NOTE: End date changed to 02/15/2024 per NSSC information (Ed., 5/26/23)		
Key Personnel Changes/Previous PI:	PI notes additional collaborators who are assisting with the project: Lahouaria Hadri, Kenneth Walsh, and Venkata Naga SrikanthGarikpati (Ed.,		
COI Name (Institution):	Kishore, Raj (Temple University School of Medicine)		
Grant/Contract No.:	80NSSC19K1079		
Performance Goal No.:			
Performance Goal Text:			
Task Description:	Ed. note 2/10/2020: Continuation of "Space Relevant Radiation-Induced Cardiovascular Disease Risk Thresholds: Effect of Gender on the Outcom During the future Moon, near Earth asteroids, and Mars missions, astronauts will be exposed to higher total doses of space irradiation (IR) (~0.4-(breast cancer has shown that the rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per Gy, with no appare cancer treatment (1.25 Gy total-body irradiated), identified seven urine-based biomarkers with distinct differences between pre- and post-exposur Hypotheses: Our central hypothesis is that low-dose proton and HZE (high energy) particle IR-induced biological responses are long-lasting, IR t radio-biologically effective (RBE) IR thresholds for CV risk estimates. Gene expression and epigenetic modifications in protein and microRNA (AIM 1. Determine the longitudinal effect of IR type, dose, and gender on cardiovascular physiology in wild type mice and ApoE null mice after f AIM 2. Determine space-type IR mediated modulations in exosomal cargo in the blood, and determine whether these changes are associated with AIM 3. Utilize known and newly identified biomarkers in the blood to develop human-relevant point-of-care tests (POCT) for predicting and mon We anticipate that the results of our proposed work may be beneficial for human space exploration and could (1) Determine single whole body m modifications in the circulating exosomal cargo contents and whether IR-induced exosomal cargo modulations are reflective of subclinical change data sets with gene expression and epigenetic data to identify biomarkers in bio-fluids that could be used for prediction of asymptomatic CVD in		
Rationale for HRP Directed Research:			
Research Impact/Earth Benefits:	We anticipate that the results of our work could be beneficial for human space exploration as well as for the Earth-based applications on several la signaling of CV alterations; (3) identify biomarkers in the blood that could be used for prediction of asymptomatic CV disease, which will include treatment of IR-induced CVDs in space and in Earth-bound civilian population, in general.		
	Our new findings for the reporting period are organized below by four sub-titles containing corresponding background, methodology, main findin Sub-project 1: Title: "Lifetime Evaluation of Cardiac Function and Structure in C57bl/6j Mice after Gamma and Space-Type Radiation Exposure" Background. The lifetime effects of space irradiation (IR) on left ventricular (LV) function are unknown. The cardiac effects induced by space-typ whole-body IR exposure; (3) establish whether dose thresholds for gamma (y) and simGCRsim IR exist; and (4) describe the comparative impact Methods. Three-month-old, age-matched, male C57BL/6J mice were irradiated with 137Cs gamma (gamma; 100, 200 cGy) and 5-ion simplified We assessed the mRNA expression of genes involved in cardiac remodeling, fibrosis, inflammation, and calcium handling in LVs harvested at 66 Main Findings. All IR groups had impaired global LV systolic function at 14, 28, and, 365 days. At 660 days, 50 cGy simGCRsim-IR mice exhib cardiac remodeling processes commonly associated with diastolic dysfunction. IR groups showing statistical significance were modeled to calcula Summary. Our work is the first to assess in mice the lifetime longitudinal effects of simGCRsim-IR at doses of 50 and 100 cGy and y-IR at doses cGy) wild-type C57BL/6J male mice as early as 14 and 28 days post IR, as well as 365 and 440 days post–IR; (2) at 660 days post IR, simGCRsi expression of markers of cardiac fibrosis (TGFB1, MMP9), inflammation (MCP-1), and hypertrophy (ßMHC), results that suggest simGCRsim-IR Sub-project 2: Title: "Lifetime Risk of Tumor Development in C57b1/6j Mice Exposed to a Single Full Body Gamma and C57B1/6J MICE EXPOSED TO A Sl Background: Radiation-induced cancer is one of the primary risks associated with exposure to space radiation (IR) during deep-space missions. T processes. Methods: As part of our NASA-funded mouse-lifetime studies to evaluate the effect of space-type and gamma (y)-IR on cardiovascular disease (C 5-ion simplified GCR simulation-IR (simGCRsim). Control ApoE null and WT mice were fed with mouse chow (normal diet-ND) and one group pathologists blindfolded to treatment conditions. Main Findings: At all time points and treatment conditions examined, a total of 9 neoplasms were detected in ApoE null mice, including ND-fed 7/17 (41%) animals developing neoplasms at 16 and 22 months, respectively. A small number of WD-fed and 100 cGy y-IR mice developed mon tumor prevalence represented by lymphoma, hemangiosarcoma, hepatoblastoma, early carcinoma (all liver) and hemangiosarcoma, lymphoma (sp in 50 cGy simGCRsim-IR WT mice. Lung tumors were not observed at 22 months in any treatment group, though hepatic and splenic tumors wer Summary: Our studies revealed that – i) the incidence of tumors is higher in WT compared to ApoE null mice after the same doses of y- and simG IR-induced internal organ tumors was higher in 100 cGy y- versus 50 cGy simGCRsim-IR, suggesting higher carcinogenic potential of y-IR at th		

lated: FY 02/27/2023

No

Fax: FY

hone: 617-480-3890

State: NY

strict: 12

ource: 2016-2017 HERO NNJ16ZSA001N-SRHHC. Appendix E: Space Radiobiology and Human Health Countermeasures Topics

Date: 02/15/2024

grees: 0

grees: 1

grees: 0

nter: NASA JSC

hone: 281-244-0596 (o)/832-221-4576 (m)

)NSSC18K0921, due to PI move to Icahn School of Medicine at Mount Sinai from Temple University. (Ed., 2/10/2020)

5/26/23).

ne," grant 80NSSC18K0921 with the same Principal Investigator Dr. David Goukassian, due to PI move to Icahn School of Medicine at Mount Sinai from Temple University.
1.5 Gy) from galactic cosmic rays (GCR). Most of what we know about harmful effects of IR on cardiovascular (CV) system is from epidemiological studies of long-term survivors of cancer radiotherapy (RT). A recent study of 2,168 women who underwent RT for nt lower or upper threshold. In this study, it was determined that average of the mean doses to the whole heart was 4.9 Gy with the range of 0.03 - 27.72 Gy. Furthermore, metabolomics studies, in patients undergoing hematopoietic stem cell (HSC) transplantation as part of e samples. The levels of these markers were found to be gender-dependent suggesting that separate biomarker signatures may exist for males and females.

ype- and dose-dependent and may augment excess relative risk (ERR) estimates for the development of cardiovascular diseases (CVDs) during and after long-duration space missions. In addition, we hypothesize that gender differences could further modify miRNA) in exosomes from the blood (e.g., plasma/serum) may be altered before the onset of the cardiac symptoms, which could be used as potential biomarkers to predict the CVD risks. We will test our hypotheses with the following specific aims:

ull-body 5-ion simplified mixed field and gamma radiation.

alterations in the heart function, structure, and vasculature before the manifestation of clinical symptoms.

nitoring possible CV alterations before and during space flights.

ixed field dose-response, radio-biologically effective IR thresholds in the heart and cardiac vasculature, and whether gender differences could modify radio-biologically effective IR thresholds for CV risk estimates; 2) Determine whether space radiation leads to s in the cells and organs of origin; 3) Ascertain if modulations of exosomal cargo may be representative of chronic oxidative stress and inflammation and could serve as early biomarkers of IR-induced CVD initiation and progression; 4) Integrate physiological CV endpoint the setting of space IR, which will include known early and intermediate biomarkers of cardiac damage, inflammation, and oxidative stress, as well as currently unknown novel radiation-associated cardiac biomarkers.

vels -- (1) determine whether low dose space-type and terrestrial IR may present an increased risk for CVD development during and after prolonged space missions, as well as after conventional and particle cancer radiotherapy; (2) determine the underlying molecular e known early and intermediate biomarkers of cardiac damage, as well as currently unknown novel cardiac biomarkers; (4) the identification of sub-clinical CV disease biomarkers that could be used for monitoring the effectiveness of mitigating factors for prevention and

gs, and the summary.

pe IR, specifically simplified galactic cosmic ray simulation (simGCRsim), are yet to be discovered. This study aimed to - (1) determine the effects of (terrestrial) and simGCRsim (space) IR on LV function; (2) identify disease spectrum and latency following single, of γ and simGCRsim IR by calculating Relative Biological Effectiveness (RBE) and Radiation Effects Ratio (RER).

GCR simulation (simGCRsim; 50, 100 cGy). LV function was assessed by transthoracic echocardiography at 14, 28 days (early), and 365, 440, 660 (late) days post-IR. We measured endothelial function markers of brain natriuretic peptide in plasma at three late time points. 0 days post IR. RBE and RER estimates were calculated for LV ejection fraction and LV fractional shortening, on which IR had a statistically significant effect.

ited preserved LV systolic function with altered LV size and mass. At this time point, simGCRsim-IR mice had elevated levels of cardiac fibrosis, inflammation, and hypertrophy markers TGFβ1, MCP1, MMP9, and βMHC, suggesting that space-type IR may induce te the Relative Biological Effectiveness (RBE) and Radiation Effects Ratio (RER). The observed dose-response shape did not indicate a lower threshold at these IR doses.

of 100 and 200 cGy on LV function and structure using echocardiography, serum biomarkers, and cardiac tissue structure alterations. Our findings can be summarized as follows: - (1) LV systolic function is impaired in simGCRsim (50, 100 cGy) and γ-IR (100, 200 n-IR male mice appear to have developed a HFpEF cardiac phenotype, though diastolic dysfunction cannot be ruled out, while the cardiac function is recovered in γ-IR mice; (3) cardiac function alterations at 660 days post IR appear to be associated with increased t may dynamically affect cardiac remodeling processes throughout a lifetime; and (4) no clear dose-response was observed.

NGLE FULL BODY GAMMA AND simGCRsim Radiation"

here is limited data in humans and in animal models for high charge and energy (HZE)-induced carcinogenesis over the murine lifetime. We hypothesize that exposure to space-type IR may increase the risk of cancer development, especially in association with aging

CVD) development, mice were examined for tumor development during scheduled tissue collections over 22 months post-IR. Three-month-old male ApoE null and C57B1/6J wild-type (WT) mice were exposed to 100 cGy of 137Cs γ-IR and 50 cGy, 500 MeV/nucleon of in each genotype was fed Western diet (WD) without IR. Note, all IR mice were fed with a ND for 22 months. All neoplasms were fully bisected with visibly unaffected tissue. Formalin-fixed tissues were submitted for routine H&E staining and evaluation by two

mice. Therefore, we focused our further studies only on WT mice. A single WT mouse developed a lymphoma in control No-IR mice at 22 months. In WT mice, the prevalence of neoplasms (liver, lung, spleen) was the highest in no-IR, WD-fed mice with 9/15 (60%) and e than one distinct tumor. At 16 months, tumors in WD-fed mice were represented by 7 liver tumors (2 - hepatocellular carcinomas, 1 - hemangiosarcoma, 4 - metastatic lymphomas), 1 lung (lymphoma), and 1 spleen (hemangiosarcoma) tumors. In WT IR mice, higher leen) was found in 100 cGy γ-IR mice 2/16 (12.5%) and 8/16 (50%) at 16 and 22 months, respectively. At the same respective time points, there were 1/15 (6.7%) and 6/15 (40%) tumors represented by lymphoma, hepatocellular carcinoma, histiocytic sarcoma (all liver) e higher in all groups.

CRsim-IR suggesting underlying genotypic variance may attenuate pathways involved in tumorigenesis; ii) the highest number of tumors during the lifetime of WT mice was detected in the WD-fed group, but not in either of IR groups, iii) in WT mice, the incidence of se doses; iv) the liver is the most affected organ by tumor growth, followed by the spleen. These results suggest that age-related metabolic changes and IR-induced mutagenesis may drive carcinogenesis.

Task Progress:	Sub-project 3: Title: "Space Radiation Induced Clonal Hematopoiesis: Lifetime Disease Susceptibility Risks and Identification of Biomarkers" Background: Recent epidemiological studies have documented the prevalence of somatic mutations within the cells of the hematopoietic system i (CHIP). The recent NASA Twin Study provided a detailed analysis of how prolonged, low-orbit space travel may contribute to genotoxic stress a leukocytes collected 21-24 years ago from 14 relatively young astronauts who flew space Shuttle missions between 1998-2001 to assay, retrospec beyond Earth's geomagnetic field where there is increased exposure to high atomic number and high energy IR. Methodology: Of particular interest to the proposed studies are findings in our preliminary mouse lifespan space IR studies. As part of our NASA after 100 cGy, of gamma (γ)- and 50 cGy (500 MeV/n) of 5-ion simplified GCR simulation (simGCRsim)-IR. Both types of IR showed deleterio in non-IR mice at 16 months and none at 22 months. To study the effects of aging and IR on the development of malignancies (hematopoietic and frequency (VAF) > 0.1%, and annotation was performed using ANNOVAR and MuTect. Main Findings: At 22 months post-IR mWES analysis revealed a higher incidence (8%) of non-frameshift deletions in both IR groups compared t common for aging and are increased after space-type exposure. Interestingly, stop-gain mutations were increased due to aging (7%) and WD-fed (hematopoietic and solid) and cardiovascular diseases. Comparing mutation-type versus cancer pathology revealed that hepatocellular carcinoma IR type include - 1) NF-kB pathway, 2) WNT/beta-catenin signaling pathway, and 3) different mediators of cell cycle checkpoints. Additional stu Summary: While the impact of space travel on CHIP is completely unknown, it is reasonable to speculate that space IR in combination with other of individual susceptibility, predictive genetic biomarkers and development of mitigation strategies before and after future deep space exploration Sub-project 4: Title: "Lifetime Evaluation of Cardiac Function and Structure in Female C57bl/6j and Apoe Null Mice after Gamma and Space-Type Radiation E Background: Space radiation (IR) from Solar Particle Events (SPE) and Galactic Cosmic Rays, also known as high charge and energy (HZE) ioni Apolipoprotein-E (ApoE) null and C57BL6/J wild type (WT) male mice exhibit reduced global systolic function at 14 and 28 days after exposure showed significant cardiac dysfunction paired with structural alterations. To assess for any sex-specific effects following IR exposure, we hypoth Methods: Three-month-old female age-matched WT and ApoE null mice were irradiated with 137Cs-γ -IR (100 cGy, 0.662 MeV) and simGCRsi clearance of elevated plasma low-density lipoproteins (LDL) levels, however, WT mice do not develop atherosclerosis. We assessed left ventricu Main Finding: At 28 days post-IR, 50 cGy simGCRsim-IR ApoE null and WT mice exhibit reduced Left ventricular ejection fraction (LVEF) and WD-fed mice and two IR groups of both genotypes. However, in WT mice LV internal diameter (LVIDd), stroke volume (SV), and LV mass wer 440-, and 580 days post-IR. Summary: Our lifetime longitudinal echocardiography findings showed minimal and not statistically significant radiation-associated alterations in after space and terrestrial IR over the lifetime of female mice. These findings do not exclude the possibility of increased acute or degenerative CV
Bibliography Type:	Description: (Last Updated: 03/06/2024)
Abstracts for Journals and Proceedings	Brojakowska A, Fish K, Khlgatian MK, Grano C, Bisserier M, Zhang S, Chepurko V, Chepurko E, Gillespie V, Dai Y, Hadri L, Kishore R, Gouk Abstracts. 2021 NASA Human Research Program Investigators' Workshop, Galveston, Texas, February 1-4, 2021. , Feb-2021
Abstracts for Journals and Proceedings	Bisserier M, Khlgatian MK, Grano C, Zhang S, Brojakowska A, Fish K, Goukassian DA, Hadri L. "Longitudinal evaluation of right ventricular c Abstracts. 2021 NASA Human Research Program Investigators' Workshop, Galveston, Texas, February 1-4, 2021. , Feb-2021
Abstracts for Journals and Proceedings	Brojakowska A, Bisserier M, Khlgatian MK, Zhang S, Gillespie V, Dai Y, Hadri L, Goukassian DA. "Lifetime risk of tumor development in c57 Abstracts. 2021 NASA Human Research Program Investigators' Workshop, Galveston, Texas, February 1-4, 2021. , Feb-2021
Articles in Peer-reviewed Journals	Bisserier M, Saffran N, Brojakowska A, Sebastian A, Evans AC, Coleman MA, Walsh K, Mills PJ, Garikipati VNS, Arakelyan A, Hadri L, Gouk
Articles in Peer-reviewed Journals	Goukassian D, Arakelyan A, Brojakowska A, Bisserier M, Hakobyan S, Hadri L, Rai AK, Evans A, Sebastian A, Truongcao M, Gonzalez C, Baj https://doi.org/10.1002/cnm2.845 ; PMID: 35653543 PMCID: PMC9162436 , Jun-2022
Articles in Peer-reviewed Journals	Bisserier M, Brojakowska A, Saffran N, Rai AK, Lee B, Coleman M, Sebastian A, Evans A, Mills PJ, Addya S, Arakelyan A, Garikipati VNS, H https://doi.org/10.3389/fcvm.2022.855181 ; PMID: 35783863 PMCID: PMC9243458 , Jun-2022
Articles in Peer-reviewed Journals	Rai AK, Rajan KS, Bisserier M, Brojakowska A, Sebastian A, Evans AC, Coleman MA, Mills PJ, Arakelyan A, Uchida S, Hadri L, Goukassian D 35811715 PMCID: PMC9276956 , Jun-2022
Articles in Peer-reviewed Journals	Brojakowska A, Kour A, Thel MC, Park E, Bisserier M, Garikipati VNS, Hadri L, Mills PJ, Walsh K, Goukassian DA. "Retrospective analysis of
Articles in Peer-reviewed Journals	Brojakowska A, Jackson CJ, Bisserier M, Khlgatian MK, Grano C, Blattnig SR, Zhang S, Fish KM, Chepurko V, Chepurko E, Gillespie V, Dai Y https://doi.org/10.3390/ijms24065451 ; PubMed PMID: 36982574; PubMed Central PMCID: PMC10049327 , Mar-2023
Significant Media Coverage	Gasparini A. (Goukassian DA interview). ""Astronaut Blood Samples Could Reveal Health Risks Posed By Space Flight". Dr. Goukassian interv
Significant Media Coverage	Howell E. (Goukassian DA interview). ""Astronauts' blood shows signs of DNA mutations due to spaceflight". Dr. Goukassian interviewed by sp
Significant Media Coverage	Byrne J. (Brojakowska A and Goukassian DA interview) "Spaceflight may be linked to somatic mutations, increased risk for cancer, heart disease Dec-2022
Significant Media Coverage	Christensen T. (Goukassian DA interview). "DNA to leak out of astronauts' cell powerhouse", American Heart Association News. Dr. Goukassian
Significant Media Coverage	Clarke V. (Goukassian DA interview). "Spaceflight can cause mutations in human DNA. Astronauts safe? Dr. Goukassian interviewed by UK Da
Significant Media Coverage	McFarland F. (Goukassian DA interview). "Astronauts' blood shows signs of DNA mutation due to spaceflight may have a cancer risk. Dr. Gouk
Significant Media Coverage	Arianne G. (Goukassian DA interview). "DNA Mutations Found In Astronauts' Blood: Study. Dr. Goukassian interviewed by Business Times rep
Significant Media Coverage	Porterfield C. (Goukassian DA interview). "Spaceflight Could Increase Risk Of Cancer And Heart Disease In Astronauts, Study Suggests. Dr. Go
Significant Media Coverage	Nikravesh I. (Goukassian DA Press Release). "Researchers Find Spaceflight May Be Associated With DNA Mutations and Increased Risk of Dev https://www.mountsinai.org/about/newsroom/2022/researchers-find-spaceflight-may-be-associated-with-dna-mutations-and-increased-risk-of-de
Significant Media Coverage	Martin M. (Goukassian DA interview). "NASA Astronauts' Blood Shows Signs of DNA Mutation After Returning From Space. Dr. Goukassian i https://finance.yahoo.com/news/nasa-astronauts-blood-shows-signs-155872841.html?guccounter=1&guce_referrer=aHR0cHM6Ly93d3cuZ29vZ , Sep-2022
Significant Media Coverage	William. (Goukassian DA interview). "NASA Astronauts' Blood Shows Signs Of DNA Mutations Due To Spaceflight And They Must Be Monit
Significant Media Coverage	Melillo G. (Goukassian interview). "Spaceflight may increase the risk of heart disease, cancer: study. Dr. Goukassian interviewed by The Hill rep
Significant Media Coverage	The Universe Today. (Goukassian DA interview). "Space travel changes astronauts' DNA. Dr. Goukassian interviewed by The Universe Today re
Significant Media Coverage	Carbone C. (Goukassian DA interview). "NASA astronauts' blood shows signs of DNA mutations due to spaceflight and they must be monitored Sep-2022
Significant Media Coverage	Quach K. (Goukassian DA interview). "Astronaut blood reveals genetic mutations for cancer and heart disease. Dr. Goukassian interviewed by Th
Significant Media Coverage	Sharma B. (Goukassian DA interview). "Study Finds Astronauts' Blood Develops DNA Mutations Due To Spaceflight. Dr. Goukassian interview
Significant Media Coverage	Antidote H. (Goukassian DA interview). "Astronauts' blood shows signs of DNA mutations due to spaceflight. Dr. Goukassian interviewed by rep
Significant Media Coverage	Leitch C. (Goukassian DA interview). "Spaceflight Seems to Raise Levels of Circulating Cell-Free Mitochondrial DNA. Dr. Goukassian intervie
Significant Media Coverage	Press Release (Goukassian DA interview). "Researchers find spaceflight may be associated with DNA mutations and increased risk of developing
Significant Media Coverage	Felicity T. (Goukassian DA interview). "Spaceflights 'Most Likely' Linked to DNA Mutations Putting Astronauts at Risk of Cancer. Dr. Goukass
Significant Media Coverage	Martin M. (Goukassian DA interview). "NASA Astronauts' Blood Shows Signs of DNA Mutation After Returning From Space. Dr. Goukassian i
Significant Media Coverage	Shirole T. (Goukassian DA interview). "Astronauts Prone to DNA Mutations That Increases Risk of Cancer and Heart Disease. Dr. Goukassian in
Significant Media Coverage	Voytovich K. (Goukassian DA interview). "Scientists have discovered mutations in the DNA of astronauts' cells. Dr. Goukassian interviewed by
Significant Media Coverage	Tangermann V. (Goukassian DA interview). "Scientists Found Genetic Mutations in Every Astronaut Blood Sample They Studied. Dr. Goukassi
Significant Media Coverage	Bayard J-G. (Goukassian DA interview). "Can spaceflight damage our DNA? Dr. Goukassian interviewed by Pourquoi Doctor reporter." Pourquo
Significant Media Coverage	Henderson E. (Goukassian DA interview). "Spaceflight increases the risk of developing cancer and heart disease. Dr. Goukassian interviewed by

n healthy individuals. These acquired DNA mutations accumulate with age and, in some instances, can provide a competitive advantage to the mutant cell thus allowing for its clonal expansion, a phenomenon known as clonal hematopoiesis of indeterminate potential
nd genomic instability in leukocytes. The observed genomic instability during and after flight suggests that the ionizing radiation (IR) exposure caused DNA damage to hematopoietic stem cells that replenish blood cells throughout life. In our recent study, we used
tively, somatic mutations in CHIP-driver genes. We identified 34 nonsynonymous SNVs in 17 known CHIP-driver genes, of which TP53 and DNMT3A were the most frequent. It is conceivable that these genetic alterations may be particularly magnified when traveling

Human Research Program/HRP-funded mouse-lifetime studies to evaluate the effects of space-type and gamma IR on cardiovascular disease (CVD) development, 3-month-old male C57BL6/J mice were systematically examined for tumor development over 22 months
is effects on the left and right ventricular structure and function. Moreover, in y- and simGCRsim-IR mice, detectable neoplasms of internal organs (liver, spleen, lungs, lymph nodes) were observed at 16- and 22 months post-IR, but only one mouse developed a lymphoma
l solid cancers) and CVD, We performed mouse whole-exome sequencing (mWES) of white blood cells and paired tumor tissues to assess somatic mutations on a focused cohort of WT mice that develop liver tumors. Somatic variants were called with a variant allele

o none in no-IR and WD-fed groups, suggesting this could be an IR-specific mutational signature. In addition, there was an age-associated increase in frameshift deletions (3%) that was increased (to 5%) in simGCRsim-IR mice, suggesting that frameshift deletions are
mice showed an additional increase (10%) in stop-gain mutation, suggesting that these types of mutations are common for aging and increased by WD. Among all treatment conditions, several genes with identified mutations were associated with various cancers
was specific for both types of IR, and histiocytic sarcoma only for space-type IR. Interestingly, hemangiosarcoma was found in WD-fed and y-IR mice but not in simGCRsim-IR mice. Common signaling pathways that were affected by aging (no-IR) or exposure to either
dies are underway to study mWES in paired tumor samples and to perform spatial transcriptomics assay (Visium) using adjacent tumor section of the paired tumor samples.

space travel-related stresses may lead to IR-specific and gene-specific accelerations of clonal hematopoiesis. Our studies identified specific somatic mutations in known CHIP "driver" genes during the lifetime of mice that could provide a framework for the identification
missions. In addition, our studies provided scientific evidence, in animal models, on whether the CHIP-related mutant clone expansions may be the shared underlying biology for space IR-associated cancer and CVD development.

xposure"

zing IR, is a primary risk associated with deep-space missions. There are limited animal and human studies on the risk of cardiovascular disease (CVD) development due to space-IR. Our longitudinal studies in male mice showed a reduction in global systolic function in
to gamma (y) and simplified GCR simulated (simGCRsim)-IR. No significant changes were observed between the control and all other remaining IR groups over the next up to 400 days of the follow-up post-IR. At 22 months, both WT and ApoE null y-IR male mice
esized similar alterations in CV function in female ApoE and WT mice following the same IR exposure.

m (25 and 50 cGy, 500 MeV/n). Control ApoE null and WT mice were fed with mouse chow (normal diet-ND) and Western diet (WD) without irradiation. ApoE null mice are predisposed to atherosclerosis development when fed a WD mouse chow due to impaired
lar (LV) function by transthoracic echocardiography at 14, 28, 365, 440, and 580 days post-IR following the same cohort of mice for each treatment condition longitudinally.

l left ventricular fractional shortening (LVFS), which paired with decreased posterior wall thickness (LVPWd) may suggest an early but mild effect of IR on systolic function. By 180-, 365-, 440-, and 580 days post-IR, no alteration in LVEF or LVFS was observed in non-IR
e minimally reduced in 50 cGy simCRsim-IR mice at 365 days suggesting possible compensation of the altered diastolic function. In female ApoE null mice, there was no significant alteration in global LV systolic function across any treatment groups at 28-, 180-, 365-,

n global systolic function or structural cardiac alterations in both female WT and ApoE null mice across any treatment group. Compared to our findings in similarly treated male mice cohort the female cohort studies showed substantially decreased in sex-specific CVD risks
D risks at lower than 25 and 50 cGy simGCGsim doses of space-type IR and/or when combined with other space travel-associated stressors.

assian DA. "Longitudinal evaluation of cardiac function and structure in apoe null and c57bl/6j mice after gamma and space-type radiation exposure." 2021 NASA Human Research Program Investigators' Workshop, Galveston, Texas, February 1-4, 2021.

ardiac function after full space radiation exposure." 2021 NASA Human Research Program Investigators' Workshop, Galveston, Texas, February 1-4, 2021.

o1/6j mice exposed to a single full body gamma and simgcrsim radiation." 2021 NASA Human Research Program Investigators' Workshop, Galveston, Texas, February 1-4, 2021.

assian DA. "Emerging role of exosomal long non-coding RNAs in spaceflight-associated risks in astronauts." Front Genet. 2022 Jan 17;12:812188. eCollection 2021. https://doi.org/10.3389/fgene.2021.812188 ; PMID: 35111205 PMCID: PMC8803151 , Jan-2022

pai A, Cheng Z, Dubey PK, Addya S, Mills P, Walsh K, Kishore R, Coleman M, Garikipati VNS. "Space flight associated changes in astronauts' plasma-derived small extracellular vesicle microRNA: Biomarker identification." Clin Transl Med. 2022 Jun;12(6):e845.

adri L and Goukassian DA. "Astronauts plasma-derived exosomes induced aberrant EZH2-mediated H3K27me3 epigenetic regulation of the vitamin D receptor." Front Cardiovasc Med. 2022 Jun 16;9:855181. eCollection 2022.

DA and Garikipati VNS. "Spaceflight-associated changes of snoRNAs in peripheral blood mononuclear cells and plasma exosomes-A pilot study." Front Cardiovasc Med. 2022 Jun 24;9:886689. eCollection 2022. https://doi.org/10.3389/fcvm.2022.886689 ; PMID:

f somatic mutations and clonal hematopoiesis in astronauts." Commun Biol. 2022 Aug 17;5(1):828. https://doi.org/10.1038/s42003-022-03777-z ; PMID: 35978153 PMCID: PMC9385668 , Aug-2023

, Lee B, Garikipati VNS, Hadri L, Kishore R, Goukassian DA. "Lifetime evaluation of left ventricular structure and function in male C57BL/6J mice after gamma and space-type radiation exposure." Int J Mol Sci. 2023 Mar 13;24(6):5451.

iew by Forbes Science Reporter." FORBES March 10, 2022. https://www.forbes.com/sites/allisongasparini/2022/03/10/astronaut-blood-could-reveal-space-flight-risks/?sh=2a85529e7d85 , Mar-2022

ace.com reporter." Space.com September 5, 2022. https://www.space.com/astronaut-spaceflight-cancer-dna-mutations-study , Sep-2022

. Ms. Brojakowska and Dr. Goukassian interviewed by HemOncologyToday." HemOnctoday December 12, 2022. https://www.healio.com/news/hematology-oncology/20221212/spaceflight-may-be-linked-to-somatic-mutations-increased-risk-for-cancer-heart-disease ,

n interviewed AHA News reporter." American Heart Association News", October 20, 2021, https://www.heart.org/en/news/2021/10/20/spaceflight-caused-dna-to-leak-out-of-astronauts-cell-powerhouse , Oct-2021

ily News reporter." UK Daily News, September 2, 2022, https://ukdaily.news/spaceflight-can-cause-mutations-in-human-dna-astronauts-safe-68485.html , Sep-2022

assian interviewed by US Sun reporter." The US Sun, September 6, 2022, https://www.the-sun.com/tech/6164149/astronauts-dna-blood-mutation-in-space/ , Sep-2022

orter." Business Times, September 6, 2022, https://www.btimesonline.com/articles/156158/20220906/dna-mutations-found-astronauts-blood-study.htm , Sep-2022

ukassian interviewed by Forbes Africa reporter." FORBES Africa, September 1, 2022, https://www.forbesafrica.com/health/2022/09/01/spaceflight-could-increase-risk-of-cancer-and-heart-disease-in-astronauts-study-suggests/ , Sep-2022

veloping Heart Disease and Cancer. Dr. Goukassian interviewed by Mount Sinai Press release office." Mount Sinai Newsroom. August 31, 2022.
veloping-heart-disease-and-cancer , Aug-2022

nterviewed by Finance.yahoo reporter." Finance.yahoo, September 11, 2022,
2xlLmNvbS8&guce_referrer_sig=AQAAAGHKBGza4wTsfcuBnCrN_-T-grOY3ccR_ZahppuSp66aZWbcDbkEmr8AG66M5NxhQK_IcMxrLiHPbz6elbeI99ItIgkWQL4BXLFLXJ5dy6sgrtYvrBVso9r5KSaNbeilmSoxtY7iQCP-t6urRhgwTKcEIrKxKdQqnqIoHgBz69LY

ored. Dr. Goukassian interviewed by NY Breaking reporter." NY Breaking, September 5, 2022, https://nybreaking.com/nasa-astronauts-blood-shows-signs-of-dna-mutations-due-to-spaceflight-and-they-must-be-monitored/ , Sep-2022

orter." The Hill, August 31, 2022, https://thehill.com/changing-america/well-being/prevention-cures/3622854-spaceflight-may-increase-the-risk-of-heart-disease-cancer-study/ , Aug-2022

eporter." Technologie et science, October 19, 2022. https://www.speakdating.io/fr-fr/activity-space-travel-changes-astronauts-dna , Oct-2022

for cancer risk, new study reveals. Dr. Goukassian interviewed by Daily Mail reporter." Daily Mail September 5, 2022. https://www.dailymail.co.uk/sciencetech/article-11182509/NASA-astronauts-blood-shows-signs-DNA-mutations-spaceflight-monitored.html ,

ne Register reporter." The Register, September 1, 2022. https://www.theregister.com/2022/09/01/astronauts_blood_space_health/ , Sep-2022

ed by IndiaTimes reporter." IndiaTimes September 10, 2022, https://www.indiatimes.com/technology/science-and-future/astronauts-blood-develops-dna-mutations-due-to-spaceflight-study-578991.html , Sep-2022

porter." Pakistan Defense, September 5, 2022, https://defence.pk/pdf/threads/astronauts-blood-shows-signs-of-dna-mutations-due-to-spaceflight.750331/ , Sep-2022

wed by LabRoots reporter." LabRoots, October 25, 2021, https://www.labroots.com/trending/space/21548/spaceflight-raise-levels-circulating-cell-free-mitochondrial-dna , Oct-2021

heart disease and cancer. Dr. Goukassian interviewed by Mount Sinai Hospital Press Release Office." The Mount Sinai Hospital / Mount Sinai School of Medicine, August 31, 2022. https://www.sciencedaily.com/releases/2022/08/220831113642.htm , Aug-2022

sian interviewed by TechTimes reporter." TechTimes, August 31, 2022, https://www.techtimes.com/articles/279921/20220831/spaceflights-most-likely-linked-to-dna-mutations-putting-astronauts-at-risk-of-cancer.htm , Aug-2022

nterviewed by MSN reporter." MSN, September 11, 2022, https://www.msn.com/en-us/health/medical/nasa-astronauts-blood-shows-signs-of-dna-mutation-after-returning-from-space/ss-AA11HK8v?li=BBnba9O , Sep-2022

nterviewed by MedIndia reporter." Medindia, September 5, 2022, https://www.medindia.net/news/healthwatch/astronauts-prone-to-dna-mutations-that-increases-risk-of-cancer-heart-disease-208504-1.htm , Sep-2022

Mezha Media reporter." Mezha Media September 13, 2022. https://mezha.media/en/2022/09/13/scientists-have-discovered-mutations-in-the-dna-of-astronauts-cells/ , Sep-2022

n interviewed by Futurism reporter." Futurism, September 6, 2022. https://futurism.com/neoscope/scientists-genetic-mutations-every-astronaut-blood-sample , Sep-2022

i doctor, FR, October 21, 2021, https://www.pourquoidocteur.fr/Articles/Question-d-actu/37603-Les-vols-spatiaux-peuvent-ils-endommager-ADN , Oct-2021

AZO Life Sciences reporter." AZO Life Sciences, September 2, 2022 https://www.azolifesciences.com/news/20220902/Spaceflight-increases-the-risk-of-developing-cancer-and-heart-disease.aspx , Sep-2022

Significant Media Coverage	Micu A. (Goukassian DA interview). "Space flight seems to be causing one specific mutation in the blood of astronauts. Dr. Goukassian intervie
Significant Media Coverage	Al Mayadeen. (Goukassian DA interview). "DNA mutation from spaceflight may increase cancer risk in astronauts. Dr. Goukassian interviewed b
Significant Media Coverage	Goyal N. (Goukassian DA interview). "Spaceflight Could Increase Risk of Cancer and Heart Disease in Astronauts. Dr. Goukassian interviewed b

ed by ZME Science reporter." ZME Science, September 7, 2022. https://www.zmescience.com/science/space-flight-astronauts-blood-mutation-22645/ , Sep-2022

y almayaden.net reporter." Almayaden.net, September 6, 2022. https://english.almayadeen.net/news/technology/dna-mutation-from-spaceflight-may-increase-cancer-risk-in-as , Sep-2022

y Industry Tap into News reporter." Industry Tap into News, September 12, 2022. https://www.industrytap.com/spaceflight-could-increase-risk-of-cancer-and-heart-disease-in-astronauts/63829 , Sep-2022